

Amendments to the Specification

Please replace the paragraph immediately under "Continuing Application Data" on page 2 with the following amended paragraph:

The instant utility application is a continuation of U.S. application 09/375,333, filed August 16, 1999, now abandoned, which claims priority to U.S. provisional patent application number 60/103,418, filed October 7, 1998, the entire contents of which is incorporated herein by reference; and the instant application is related to copending utility applications U.S.S.N. _____ and _____ 09/374,958, now U.S. patent 6,677,432, and 09/374,936, now U.S. patent 6,846,906 (Attorney Docket Nos. STK-076 and STK-077) filed on even date ~~herewith~~ with U.S. application 09/375,333 and also based on the aforementioned provisional application, the disclosures of which are incorporated herein by reference.

Please replace the last paragraph on page 24 with the following amended paragraph:

Figure 4 lists the aligned C-terminal residues defining the finger 2 sub-domain for various known members of the BMP family (SEQ ID NOs: 1-35 and 55), and TGF- β superfamily of proteins, starting with the first residue following the cysteine doublet.

Please replace the first paragraph on page 25 with the following amended paragraph:

Figures 5A, 5B, and 5C are single letter code listings of amino acid sequences, arranged to indicate alignments and homologies of the finger 1, heel, and finger 2 regions, respectively, of the currently known members of the TGF- β superfamily. Shown are the respective amino acids comprising each region of human TGF- β 1 through TGF- β 5 (the TGF- β subgroup) (SEQ ID NOs: 40-44), the Vg/dpp subgroup consisting of dpp (SEQ ID NO: 45), Vg-1 (SEQ ID NO: 46), Vgr-1 (SEQ ID NO: 47), 60A (SEQ ID NO: 48) (see copending U.S.S.N. 08/271,556), BMP-2A (also known in the literature as BMP-2) (SEQ ID NO: 49), dorsalin (SEQ ID NO: 54), BMP-2B (also known in the literature as BMP-4) (SEQ ID NO: 51), BMP-3 (SEQ ID NO: 50), BMP-5 (SEQ ID NO: 52), BMP-6 (SEQ ID NO: 53), OP-1 (also known in the literature as BMP-7) (SEQ ID NO: 55), OP-2 (SEQ ID NO: 56) (see PCT/US91/07635 and U.S. Patent No. 5,266,683) and OP-3 (SEQ ID NO: 57) (U.S.S.N 07/971,091), the GDF subgroup consisting of GDF-1 (SEQ ID NO: 58), GDF-3 (SEQ ID NO: 59), and GDF-9 (SEQ ID NO: 60), the Inhibin subgroup consisting of Inhibin α (SEQ ID NO: 61), Inhibin β A (SEQ ID NO: 62), and Inhibin β B (SEQ ID NO: 63). The dashes (-) indicate a peptide bond between adjacent amino acids. A consensus sequence pattern for each subgroup is shown at the bottom of each subgroup.

Please replace the second paragraph on page 25 with the following amended paragraph:

Figure 6 is a single letter code listing of amino acid sequences, identified in capital letter in standard single letter amino acid code, and in lower case letters to identify groups of amino acids useful in that location, wherein the lower case letters stand for the amino acids indicated in accordance with the pattern definition key table set forth in Figure 3. Figure 6 identifies preferred pattern sequences for constituting the finger 1, heel, and finger 2 regions of biosynthetic constructs of the invention (SEQ ID NOs:64-67). The dashes (-) indicate a peptide bond between adjacent amino acids.

Please replace the third paragraph on page 25 with the following amended paragraph:

Figure 7(A) shows the nucleotide and corresponding amino acid sequences of H2487 (SEQ ID NOs: 89 and 90), a modified OP-1 comprising N-terminal decapeptide collagen binding site inserted upstream of the seven-cysteine domain.

Please replace the fourth paragraph on page 25 with the following amended paragraph:

Figure 7(B) shows the nucleotide and corresponding amino acid sequences of H2440 (SEQ ID NOs: 91 and 92), a modified OP-1 comprising a hexa-

histidine domain attached 35 residues upstream of the first cysteine in the seven-cysteine domain.

Please replace the first paragraph on page 26 with the following amended paragraph:

Figure 7(C) shows the nucleotide and amino acid sequences of H2521 (SEQ ID NOs: 93 and 94), a modified OP-1 comprising an FB leader domain of protein A attached 15 residues upstream of the first cysteine in the seven-cysteine domain.

Please replace the second paragraph on page 26 with the following amended paragraph:

Figure 7(D) shows the nucleotide and amino acid sequences of H2525 (SEQ ID NOs: 95 and 96), a modified OP-1 comprising both an FB leader domain of protein A and a hexa-histidine domain.

Please replace the third paragraph on page 26 with the following amended paragraph:

Figure 7(E) shows the nucleotide and amino acid sequences of H2527 (SEQ ID NOs: 97 and 98), a modified OP-1 comprising an FB leader domain, a hexa-histidine domain, and an ASP-PRO acid cleavage site.

Please replace the fourth paragraph on page 26 with the following amended paragraph:

Figure 7(F) shows the nucleotide and amino acid sequences of H2528
(SEQ ID NOs: 99 and 100), a modified CDMP-3 comprising an FB leader
domain and a hexa-histidine domain.

Please replace the fifth paragraph on page 26 with the following amended
paragraph:

Figure 7(G) shows the nucleotide and amino acid sequences of H2469
(SEQ ID NOs: 101 and 102), a modified OP-1 (truncated) comprising 14
original residues upstream of the first cysteine in the conserved seven-
cysteine domain.

Please replace the sixth paragraph on page 26 with the following amended
paragraph:

Figure 7(H) shows the nucleotide and amino acid sequences of H2510
(SEQ ID NOs: 103 and 104), a modified OP-1 comprising a collagen
binding site inserted 7 residues upstream of the first cysteine in the
conserved seven-cysteine domain.

Please replace the seventh paragraph on page 26 with the following
amended paragraph:

Figure 7(I) shows the nucleotide and amino acid sequences of H2523
(SEQ ID NOs: 105 and 106), a modified OP-1 comprising a collagen
peptide and a spacer added 13 residues upstream from the first cysteine in
the conserved seven-cysteine domain.

Please replace the eighth paragraph on page 26 with the following amended paragraph:

Figure 7(J) shows the nucleotide and amino acid sequences of H2524 (SEQ ID NOs: 107 and 108), a modified OP-1 comprising a hexa-histidine domain, a collagen peptide and a spacer added 13 residues upstream from the first cysteine in the conserved seven-cysteine domain.

Please replace the second full paragraph on page 76 with the following amended paragraph:

The mutant proteins of the present invention exhibit improved biological activity as well as extended half-life. Further, increased activity observed with the truncated proteins of the present invention may be due to elimination of basic residues and/or the lowering of the protein's isoelectric point. Biological activity and improved refolding can be enhanced when the modified proteins of the present invention are combined with the modifications described in co-pending applications [Atty Docket No. STK-076, filed on August 16, 1999] and [Atty Docket No. STK-077, filed on August 16, 1999], the disclosures of which are incorporated herein by reference.